embodiment, the method further comprises the step of amplifying the immobilized probe and then detecting resultant amplified probe. In a more particular embodiment, the method further comprises the steps of releasing and amplifying the probe to produce a labeled, amplified double-stranded probe, hybridizing the labeled probe to a target polynucleotide to immobilize the labeled probe and detecting the labeled probe, particularly wherein the probe is double-stranded and target is single-stranded.--

IN THE CLAIMS

In claim 1, line 3, please delete "at least".

In claim 3, line 1, please change "isolating" to --releasing--.

REMARKS

Drawings

Corrected drawings are being mailed today under separate cover to the Draftsperson.

Amendments

The specification is amended to correct spelling mistakes, complete a citation by referencing a prior usage of the same citation, and provide a brief description of the relevant subject matter of each of the cited references. These same amendments were made in copending 09/449,059. The specification has also been amended to correct typographical errors kindly noted by the Examiner. The insertion at p.10 is a restatement of claims 3-7 as filed. Claim 1 has been amended to delete the superfluous "at least". Claim 3 has been clarified to use the same "releasing" term as claims 6 and 7. These amendments introduce no new matter.

35USC112, first paragraph

The Action has applied an enablement rejection to claims 1-24 for encompassing steps recited in dependent claims 3-7; namely, (1) isolating the immobilized probe, (2) amplifying the immobilized probe and then detecting resultant amplified probe, and (3) releasing and amplifying the probe. The issue is whether the specification enables one of ordinary skill in this art to practice the invention as claimed without undue experimentation.

Claims 1, 2, 8-24 do not recite the objected-to steps. In fact, claim 1 requires only a single step: combining a polynucleotide probe with a polynucleotide target stably associated with a surface of a solid support, wherein one of the probe and target is double-stranded comprising complementary strands, and the other is single-stranded having complementarity with one of the complementary strands, under conditions wherein the probe and target hybridize and the probe is thereby immobilized. Every aspect of this claimed method is amply described, including methods for making the probes (p.8, line 12 - p.9, line 10) and targets (p.6, line 19 - p.7, line 22); methods for stably associating the targets to a solid support surface (p.7, line 23 - p.8, line 11) and conditions for hybridizing the probe to the immobilized target (p.10, lines 5-8). In addition, the entire method is repeatedly exemplified in experimental detail (p.12, line 5 - p.18, line 10). There is no evidence or even suggestion that the recited method step is not enabled, described and exemplified: rather, the Action suggests that the claim can encompass other steps (the claims use the "comprising" transitional word) and that these additional steps are not enabled. For the reasons explained below, we believe the additional steps recited in claims 3-7 are enabled and claims 1, 2, 8-24 are enabled for these same reasons. Furthermore, we also believe the rejection is legally inapplicable to claims 1, 2, 8-24, as these claims do not recite the objected-to steps.

Any method claim using the "comprising" preamble encompasses an infinite number of embodiments. A method "comprising step A" technically encompasses a method wherein step A is followed by a triple back flip. Yet the Action does not protest that one of ordinary skill in the art of solid phase biochemistry could not perform such a gymnastic feat without undue experimentation. The enablement inquiry is properly directed to the method as recited by the claim - not to every conceivable compound-activity which could be encompassed by an open method claim.

In this case, though, the additional steps recited in dependent claims 3-7 are readily practiced by one of ordinary skill in the art without undue experimentation. For example, claim 3 is the method of claim 1 further comprising the step of releasing the immobilized probe. This is trivial - the additional step merely requires subjecting the probe to conditions whereby it would be released from the immobilized target. Conditions for hybridizing and dehybridizing polynucleotides are routine, well-known in the art and involve no more than adjusting temperature and/or salt concentrations (e.g. Maniatis et al., cited on p.10, line 6; see also, p.17,

line 11). The specification readily enables those skilled in the art to hybridize the probe to the immobilized target; with or without our specification, they are readily able to dehybridize it.

Claim 4 is the method of claim 1 further comprising the step of amplifying the immobilized probe. Methods for amplifying a given polynucleotide are routine and well-established (e.g. Maniatis et al., cited on p.8, line 22); amplification is in fact how the probes are generally made (p.8, line 28) – the targets too (as amplified PCR elements, p.17, lines 4-5).

Claim 5 is the method of claim 1 further comprising the step of amplifying the immobilized probe and then detecting resultant amplified probe. The additional step (over claim 4) of detecting the amplified probe is routine: methods for labeling amplified probes are described (p.8, lines 27-28) as are methods for detecting them (p.10, lines 8-11).

Claim 6 is the method of claim 1 further comprising the steps of releasing and amplifying the probe to produce a labeled, amplified double-stranded probe, hybridizing the labeled probe to a target polynucleotide to immobilize the labeled probe and detecting the labeled probe. The additional step (over claims 3 and 5) of hybridizing the probe to an immobilized target polynucleotide requires no more than repeating the step of claim 1. Hybridizing probes to immobilized targets is thoroughly described and exemplified (see e.g. Examples 1 and 2).

Claim 7 is the method of claim 1 further comprising the steps of releasing and amplifying the probe to produce a labeled, amplified double-stranded probe, hybridizing the labeled probe to a target polynucleotide to immobilize the labeled probe and detecting the labeled probe, wherein the probe is double-stranded and target is single-stranded. The additional limitation (over claim 7) is the requirement that the probe is double-stranded and target is single-stranded, as exemplified in Examples 3-10.

How to isolate or release an immobilized probe, how to amplify such probe and how to detect an amplified probe are all trivial tasks to those skilled in the art of solid phase hybridization assays. The Action's suggestion that it would require several years to perform these tasks is without support. While the Action does not provide any evidence supporting a prima facie case that the claims are not enabled, to expedite prosecution, Applicants provide affirmative evidence in the form a Declaration of Mark Reynolds, an expert with over 17 years experience in solid phase hybridization methods. Dr. Reynolds explains, *inter alia*, that the teachings and exemplification of the specification fully enable one of ordinary skill in the art to

practice the methods recited in claims 3-7 without undue experimentation. In particular, the specification enables one of ordinary skill in the art, without requiring any undue experimentation, to release and amplify the recited immobilized probe, to label the resultant amplified probe, and to then hybridize the labeled probe to a target polynucleotide to immobilize the labeled probe, and to detect the labeled probe. Accordingly, both the Application and the uncontroverted evidence of record establish that the claims are enabled and in compliance with 35USC112, first paragraph.

35USC102(b)

The claims encompass a solid phase hybridization assay: an immobilized target hybridizes with a probe, wherein one of the two is double-stranded and the other is single-stranded. The single-stranded molecule is complementary to one of the strands of the double-stranded molecule, i.e. it has the complementary sequence and opposite orientation as one strand and the same sequence and orientation as the other strand of the double-stranded molecule (see p.5, lines 22-24).

This structural requirement is neither met nor suggested by the cited art, which relates to an entirely different kind of polynucleotide binding called Hoogsteen binding. The cited Bates et al. (Nucleic Acids Res. 23, 3627-3632, 1995) describes Hoogsteen triplex formation (p.3628, col.1, line 16). The triplex-forming molecules and reaction are shown in Table 1. The cited reactions are (1)Bt-T30/A30/T30, (2)Bt-AY/AU/Pso-20 and (3)Bt-HD1/HD2/HD3. Figure 2 describes each of these molecules: in each case, you have the third single stranded molecule binding the backside of the purines of the immobilized double stranded molecule. Note that the third strands are always pyrimidine polymers (T30, Pso-20 or HD30; see Fig.2). There is no complementarity[1], as expressly required by our claims. Bates's solid phase Hoogsteen binding assay provides a useful system for studying the kinetics of this phenomenon, however it is inapplicable to other than pyrimidine probes and purine rich targets and it is not a hybridization

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[1] Note that even with Bates' polyT/polyA homopolymers, the orientation of the polyT probe binding is parallel (not complementary) with the polyA of the duplex (see Fig.2) and the polyA probe binding of the A30-A30-T30 triplex (p.3630) is antiparallel with the polyA - not with the polyT.

assay as claimed. Absent such a prior art teaching or suggestion, the claims are in compliance with 35USC102 and 103.

35USC103(a)

This art rejection cites Tyagi et al. (Nature Biotech. 14, 303-308, 1996), Brown et al. (US Patent No. 5,807522), Pease et al. (Proc. Natl. Acad. sci. USA 91, 5022-5026, 1994) and Ellouze et al. (J. Biochem. 121,521-526, 1997), but relies exclusively on Ellouze for suggesting a triplex assay. Like Bates, Ellouze is a polyT-polyA-polyT Hoogsteen binding assay (see line 10 of Abstract) in which a homo-pyrimidine polymer (polyT) binds the backside of a parallel homo-purine strand - again, the binding involves no complementarity. Combining Ellouze with Brown and Pease would yield a solid phase Hoogsteen binding assay such as described by Bates; adding Tyagi would introduce fluorescent labels. Nowhere described or suggested is the claimed solid phase hybridization assay involving triplex formation by hybridization between complementary targets and probes. Absent such a prior art teaching or suggestion, the claims are in compliance with 35USC102 and 103.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

Applicants hereby petition for any necessary extension of time pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any fees or credit any overcharges relating to this communication to our Deposit Account No. 19-0750 (order no. IN-0016-1).

Respectfully submitted,
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Lockhart, D. J. et al. (1996; Nat. Biotech. 14:1675-1680); first page only;
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132 Declaration, 3 p.